w 30% is recorded, and the figures fall in the range ully regarded as normal (35-75%).[5] Similarly, the ıp of hospital patients selected as "normals"—i.e., e without overt malignant tumours—show counts in range accepted as normal, except for 1 patient in whom ormally low counts (20%, 28%) were registered. (This ent had been treated for a benign breast lesion.)

The majority of patients in both the breast-carcinoma other malignant-tumour groups had undergone radio- apy treatment. 4 patients in the other malignant- tour group had not received radiotherapy; they had a chromatin count in the range 30-50%. 11 patients a breast carcinoma had not undergone radiotherapy; f these had a sex-chromatin count below 20%.

DISCUSSION

Faulty technique has often been implicated in posedly abnormal sex-chromatin counts; and, because the artefacts which can be introduced by technical ors in collection, staining, and counting of the nuclear chromatin, standard techniques were adhered to dly, and considerable care was taken in the counting cedures. We believe that the abnormal counts orted here are real, particularly since the other groups l sex-chromatin counts in the accepted normal range. In genotypic females the sex-chromatin count falls hin a well-defined range. Hitherto, apart from isolated tances,[6 7] deviations from this range have been accom- nied by a change in number or form of the X chromo- nes; and the concept that deviations from the normal ues in sex-chromatin count were associated with genetic tors seemed well established. In the present work, :omosome studies by the method of Moorhead et al.[8] re performed on 4 patients with low sex-chromatin ants and no karyotypic abnormalities were demonstrated. l patients with a low sex-chromatin count were enotypically normal females.

The present results are open to several interpretations. Firstly, these patients may have a deletion of part or of one X chromosome either as a result of the disease or ssibly from treatment (radiotherapy or cytotoxic drugs). nis explanation is unlikely to be correct, especially in ew of the results of the chromosome studies. Radiation is dikely to be responsible for the production of the normal sex-chromatin counts, since abnormal counts ere not apparent in patients with other malignant mours who had been irradiated, but were apparent in tients with breast cancer who had not been irradiated. arthermore in none of 4 patients with breast cancer in hom sex-chromatin counts were made before and after diotherapy was any change in the count observed.

Secondly, these patients might represent a susceptible ubset of the population in whom some abnormality in the uclear membrane or sex-chromatin material is coupled ith a predisposition to breast cancer. If this hypothesis ere valid, one would expect to find a limited number of ndividuals in the normal population in whom a low sex- romatin count coexisted with an apparently morpho- gically normal X-chromosome status. Since no large urvey of sex-chromatin counts from a normal population as been published, this possibility cannot be excluded.

The third possibility is that the tumour itself induces a systemic effect, one feature of which is a change in the nuclear membrane or X chromosome. Those patients with breast cancer having a low sex-chromatin count might correspond to patients reported [9] as having low æticocholanolone levels, and hence this sex-chromatin abnormality might act as a marker for prognosis of the disease. Investigations to test this possibility are already in progress.

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Request for reprints should be addressed to L. J. O. at the Department of Surgery, Queen Elizabeth Hospital, Woodville, South Australia.

M. A. STANLEY
PH.D. Brist.
D. A. BIGHAM
B.SC. Adelaide
R. I. COX
PH.D. Edin.
J. A. KIRKLAND
M.D. St. And.
L. J. OPIT
M.B. Adelaide, F.R.C.S.

Departments of Obstetrics and Gynecology and of Surgery, University of Adelaide

DIETARY EFFECTS ON SERUM-PHYTANIC-ACID LEVELS AND ON CLINICAL MANIFESTATIONS IN HEREDOPATHIA ATACTICA POLYNEURITIFORMIS

HEREDOPATHIA atactica polyneuritiformis (H.A.P.) was defined as a clinical entity in 1945 by Refsum.[9] Hemeralopia and constriction of the visual fields appear to be the earliest clinical manifestations of this chronic disease which, in an irregular course with exacerbations and remissions, is associated with progressive paresis of the extremities, muscular atrophy, areflexia, cerebellar ataxia, sensory disturbances, retinitis pigmentosa, ichthyosis and electrocardiographic signs of cardiac involvement. Sudden death has occurred in some of the approximately 40 cases of H.A.P. (Refsum's disease) so far reported. The disease is genetically determined and shows a recessive mode of inheritance.

The discovery by Klenk and Kahlke [10] that these patients accumulate substantial amounts of a branched-chain fatty acid, phytanic acid (3,7,11,15-tetramethyl-hexadecanoic acid), in serum and tissue lipids has placed the condition among the "lipid storage" diseases. Our isotopic studies indicate that there is little or no endogenous synthesis of phytanic acid in H.A.P. and that the metabolic defect lies on the degradative side.[11-13] The nature of this biochemical defect has been studied.[13-16] The 3-methyl group of phytanic acid makes it resistant to ordinary β-oxidation, but degradation by ω-oxidation followed by β-oxidation could be envisaged. In 3 patients with H.A.P., the tricaprin loading test repeatedly demon-

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strated a very low ω-oxidation capacity. However, their ability to ω-oxidise cholesterol, α-tocopherol, geraniol, and 2,2-dimethylstearic acid was found to be comparable with that of normal controls. From experiments in which labelled 3,6-dimethyl octanoic acid-8-^{14}C (which can be degraded neither by β-oxidation nor by ω-oxidation followed by β-oxidation) was administered, it was concluded that there is an alternative metabolic pathway for the degradation of branched-chain fatty acids—a pathway which differs from the β-oxidation, ω-oxidation, and the isovaleric-acid degradation pathways. In 2 patients with H.A.P. a block was observed in this metabolic route.[15]

Both in animals [17] and in man, including subjects with H.A.P.,[15 18] it has been shown that orally administered phytol is readily converted to phytanic acid. In normal rats, the feeding of either phytol [17] or phytanic acid [19 20] in sufficiently large doses leads to accumulation of phytanic acid in the tissues.

In January, 1965, when preliminary experimental results indicated that the phytanic acid accumulating in H.A.P. was of exogenous origin, we instituted a closely controlled restriction in the dietary intake of foods containing phytol and phytanic acid in 2 patients. We report that both patients have shown a remarkable drop in their plasma-phytanic-acid concentrations, and 1 has shown indications of clinical improvement.

CASE-RECORDS

CASE 1.—A 25-year-old man had developed disturbances of gait and itching, dry, scaling skin at the age of 7 years, when examination at Oslo University Hospital had revealed slight impairment of hearing and signs of moderate ataxia and peripheral polyneuropathy; ophthalmological examination had revealed changes of the type found in tapetoretinal degeneration. These findings led to the diagnosis of H.A.P. Since then the condition has progressed slowly, but with remissions and relapses. Clinical examination in January, 1965, showed typical retinitis pigmentosa with hemeralopia and constriction of the visual fields, muscular atrophy, bilateral foot-drop, and absent tendon reflexes. Superficial sensation was decreased in all modalities. Joint sense and stereognosis were much impaired. There was ataxia of all extremities with unsteady gait. Electrophysiological studies showed gross decrease of conduction velocity (of the order of 7–8 metres per second in several nerves). The protein content of the cerebrospinal fluid (C.S.F.) was increased (124 mg. per 100 ml.). In addition, there was a slight increase in the total serum-protein value (7·8 g. per 100 ml.) as well as an increase in the M ("19 S") component (5·8%) of serum.[18] Intellectual capacity was normal.

CASE 2.—A 46-year-old woman, who is a member of one of the families originally studied by Refsum,[9] had been admitted to the Department of Neurology, University of Oslo, in 1951, 1964 and 1965. Over this period there developed a pronounced constriction of the visual fields with atypical retinitis pigmentosa, and impairment of hearing. The signs of cerebellar ataxia and polyneuropathy, which in 1951 were pronounced, had improved considerably in 1964 with reversion to normal of the deep tendon reflexes, which were absent in 1951. Also the protein content of the C.S.F., which in 1951 was much increased, was normal in 1964. In 1952 she developed a psychosis of a paranoid type, and in 1953 was admitted to a mental institution, where she stayed until admission to Rikshospitalet in 1964. The reason for her clinical improvement over the years is not clear, but the low vegetable and fruit content of an institutional diet may be relevant.

METHODS

Diet

The test diet was instituted in both subjects in January, 1965. Case 1 was followed as an outpatient. He kept a detailed food diary and adhered closely to the prescribed diet. Case 2 was given her diet under hospital supervision, first in the mental hospital and, since March 1965, in the Department of Neurology, University of Oslo.

In formulating the diet, an attempt was made to exclude so far as possible all foods containing chlorophyll, with its known phytol content, and also other foods that might contain phytol, phytanic acid, or their precursors. In the absence of adequate analytic data, *all* vegetables and *all* fruits were omitted. Since phytanic acid has been demonstrated in butter fat,[21] this also was omitted, and plant margarines, which by our analyses were found to be devoid of phytanic acid, were given instead. Since phytanic acid has also been found in ruminant fats,[22] the patients were asked to remove all visible fat from their meats. No attempt was made, however, to avoid animal fat in processed meats, and there were no restrictions with respect to fish, potatoes, eggs, milk, cream, and cheese. Thus, the diet was not completely devoid of exogenous precursors, but was presumably much poorer in these than the previous diet.

The diet was fortified with average daily requirements of water-soluble vitamins (ascorbic acid, thiamine, and pyridoxine). Since it was felt that some type of competition might exist between phytanic acid (or the corresponding aldehyde or alcohol) and the structurally related fat-soluble vitamins, vitamins E and A were given in therapeutic doses (100 mg. of α-tocopherol acetate and 25,000 I.U. of vitamin-A acetate daily).

Analytical Methods

The total phytanic-acid concentration of serum was determined as follows:

To the chloroform–methanol extract of 2 ml. of serum was added 1 mg. of pentadecanoic acid as an internal standard. The extracted lipids were saponified in 5 ml. of 2% sodium hydroxide in 96% ethanol for two hours. Nonsaponifiable lipids were first extracted, and then, after acidification with 5 ml. 0·5 *N* hydrochloric acid, the fatty acids were extracted with 5 portions of 5 ml. petroleum ether (b.p. 40–60°C). The fatty acids were converted to methyl esters with diazomethane and analysed by gas-liquid chromatography (8% butanediol succinate on 'Chromosorb W,' 100–120 mesh; 180°C; nitrogen carrier gas). The relative retention-time of methyl phytanate in this system corresponds to a carbon number of 16·9.

The phytanic-acid concentration was also determined in various lipid fractions of serum after isolation by thin-layer chromatography ('Silica Gel G', Merck), developed with petroleum ether (b.p. 60–80° C)/diethyl ether/acetic acid (85/15/1).

RESULTS

Fig. 1 shows the effect of the described dietary restrictions on total serum-phytanic-acid. In January, 1965, the total serum-phytanic-acid concentrations were 37 mg. per 100 ml. and 26 mg. per 100 ml. in cases 1 and 2 respectively. During the first seven or eight months on the diet, no striking change was observed. However, during the following several months a dramatic fall occurred. Phytanic-acid levels in January, 1966, had dropped to values 20–35% of those observed a year earlier. The phytanic-acid concentrations in serum-lipid subfractions were also determined. Since essentially identical results were obtained in both patients, only the data for case 1 are presented (fig. 2). Most of the serum-phytanic-acid was

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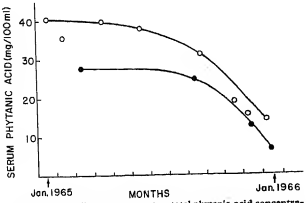

Fig. 1—Effect of dietary treatment on total phytanic-acid concentration of serum-lipids in 2 patients with heredopathia atactica polyneuritiformis: case 1 (o——o) and case 2 (•——•).

present in triglycerides and phospholipids, the concentration in the former being twice that in the latter. In both fractions the changes in phytanic-acid concentrations generally paralleled those in the total-serum-phytanic-acid concentration. Small but significant concentrations of phytanic acid were also found in cholesterol esters (approximately 1 mg. per 100 ml.) and in free fatty acids (0·5–2·0 mg. per 100 ml.). However, in these lipid fractions the phytanic-acid concentration did not change appreciably during the period of observation.

In case 2, who in January, 1965, had already shown pronounced clinical improvement relative to her condition in 1951, no further improvement was noted during the

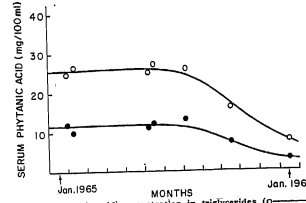

Fig. 2—Phytanic-acid concentration in triglycerides (o——o) and in phospholipids (•——•) during dietary treatment of case 1.

year on restricted diet. However, her psychotic condition makes clinical evaluation difficult.

In case 1, the condition in January, 1966, was unchanged with regard to hemeralopia (as shown by dark-adaptation curves), constriction of the visual fields, muscular atrophy, tendon reflexes, superficial sensation, and stereognosis. The protein content of the C.S.F. as well as the slightly increased concentration of macroglobulin in serum was unchanged. The degree of paresis and ataxia is difficult to estimate, but our clinical impression is that the ataxia has improved definitely and that the pareses may have improved slightly. This accords with the patient's own evaluation of his condition: "I do the various tasks of daily living easier and better than a year ago, even though I have not been particularly able to expand my activities." Objective evidence of clinical improvement has come from periodic measurements of peripheral-nerve-conduction velocity, which increased steadily during the year. This is illustrated by the values recorded for the ulnar nerve: January, 1965, 7–8 metres per second; October, 1965, 14 metres per second; January, 1966, 19 metres per second.

DISCUSSION

These data show clearly that serum-phytanic-acid levels in both subjects fell notably during a year on the restricted diet, and it seems likely that the observed fall reflects reduction of the daily intake of phytanic acid or its precursors. The findings accord with, and corroborate, the isotopic studies indicating that phytanic acid in these patients is of exogenous origin.[13 18] The decrease in serum concentration in itself does not necessarily establish that the total body stores of phytanic acid were reduced; transfer from serum compartment to tissue compartments might have occurred. However, our isotope studies show that, while the capacity of these patients to oxidise phytol and/or phytanic acid is reduced, they apparently do retain some capacity to metabolise it.[18] Furthermore, it has been shown that rats in which high tissue concentrations of phytanic acid have been built up by chronic feeding of phytol or phytanic acid eliminate these stores rather rapidly when returned to a normal diet.[17 18] The long lag period between institution of the diet and fall in serum-phytanic-acid concentration may be attributable to transfer of phytanic acid from readily-mobilised tissue stores into the serum compartment. Gas-liquid chromatographic analysis of a subcutaneous fat biopsy from case 1 in January, 1966, showed that phytanic acid represented 0·7% of total fatty acids in the depot fat. Unfortunately no earlier analyses are available.

In one subject, concomitantly with the fall in phytanic-acid concentration in the serum, there was a pronounced improvement in nerve conductivity and some apparent improvement in ataxia and muscular performance. However, most of the neurological symptoms and signs did not change significantly. In view of their chronic long-standing nature, some of the neurological deficits may be essentially irreversible, but this preliminary evidence of clinical improvement warrants further study of the present diet. These observations strongly suggest that accumulation of phytanic acid in patients with H.A.P. is related to the diet and that, to some extent, the accumulation of the abnormal acid may be of pathogenetic significance.

LORENTZ ELDJARN
M.D., PH.D.
KENNETH TRY
M.D.

Institute of Clinical Biochemistry, University of Oslo, Rikshospitalet, Oslo, Norway

ODDVAR STOKKE
M.D.
ANDERS W. MUNTHE-KAAS
M.D.

Department of Neurology, University of Oslo, Rikshospitalet, Oslo, Norway

SIGVALD REFSUM
M.D., PH.D.
DANIEL STEINBERG
M.D., PH.D.
JOEL AVIGAN
PH.D.

Laboratory of Metabolism, National Heart Institute, Bethesda, Maryland

CHARLES MIZE
M.D., PH.D.

Reviews of Books

Teaching Hospital and Medical School, Leeds: Planning Report 1965.

Sir DONALD KAERRY, BT., T.D., M.P., chairman, Board of Governors, United Leeds Hospitals, and chairman, Joint Planning Committee. Leeds: Board of Governors, United Leeds Hospitals, and the Council of the University of Leeds. 1965. 50s.

THE board of governors of the United Leeds Hospital and the University of Leeds are faced with phasing the development of a 44-acre site in the centre of Leeds for a medical school and teaching hospital, preserving but a few of the existing buildings. This volume records in considerable detail how the problem has been tackled and the conclusions. It represents three years work of a professional planning team working very closely —indeed, in the same group of offices—with a design team of the Building Design Partnership, in such a way that the brief and the design implications have emerged simultaneously. The result, unlike many other planning documents, is a most informative and readable work. Detailed studies have been made of both internal and external communications, site limitations, and essential services.

The planners, while not going all the way to a balanced hospital community on the McKeown pattern, nevertheless do see that the teaching hospital has a role beyond the traditional: for instance, by including large psychiatric, geriatric, and reablement departments, they hope to promote cooperation between general practitioners, local authority, and hospital, thus demonstrating to students the total resources of health care. There has clearly been an attempt to break down the barriers of departmental autonomy and create interdependence. Centralisation of operating-theatres, X-ray services, and central sterile supply, a self-contained isolation unit, and a modified form of progressive patient-care are planned. An interesting provisional decision is to supply catering services through a system whereby food is prepared centrally but cooking (or reheating frozen food) is done in kitchens adjoining groups of related wards.

The design is to be of low compact form. The planners hope that much of the building will be suitable for industrialised building methods, and that future expansion will be largely provided for by the possible addition of a floor. A cost comparison has been made with the more traditional narrow slab block form on a finger plan; very little difference in capital costs is disclosed, the extra cost of services being balanced by savings in structure and fabric. The running-cost will be marginally higher in the design proposed; but this, it is claimed, will be offset by improved environmental conditions for patients and staff.

Personality and Personal Illness

G. A. FOULDS, in collaboration with T. M. CAINE. London: Tavistock Publications. 1965. Pp. 344. 55s.

THE unsatisfactory nature of psychiatric classification is sometimes made the excuse for discarding Kraepelinian syndromal classification altogether. The authors make a reasonable case for retaining it in combination with a personality classification. They argue that all "personal illnesses" may be regarded as "lying along a continuum of increasing degrees of failure to maintain and establish mutual personal relationships". Drawing a distinction between personality traits and attitudes on the one hand, and symptoms and signs on the other, they applied a questionary, designed to measure the hysteroid/obsessoid traits, and a symptom-sign inventory, to several groups of psychiatric patients. The test results were compared with clinical diagnostic findings and therapeutic results. They found that tests distinguish between neurotic and psychotic, and between groups of psychotics, but are of little help in differentiation between groups of neurotics. They suggest that a more useful mode of differentiation between neurotics may be found in the preponderance either of "somatic" or of "psychic" complaints by the patient.

Alcoholism

Dr. NEIL KESSEL and Dr. HENRY WALTON. London: Penguin Books. 1965. Pp. 192. 4s.

IN less than 200 pages this little book, written by two psychiatrists working in Scotland, deals concisely and comprehensively with the complex problem of alcoholism. In Britain in 1963 the level of spirit drinking was the highest for forty years. The fact that alcoholism is a bigger problem in Scotland than in England is reflected in the admission figures for alcoholism and alcoholic psychosis, which in Scotland (a few years ago) were seven times as high in men, and five times as high in women. In a foreword Prof. G. M. Carstairs rightly says that this book can be expected to contribute much towards the better understanding of alcoholism by both public and doctors.

Textbook of Medical Treatment (10th ed. Edinburgh: E. & S. Livingstone. 1966. Pp. 1003. 70s.).—Textbooks, we are told, are on their way out. They have become out of date by the time they are published. They are "last attempts to enshrine a belief in the immutability of knowledge". Undaunted, some textbooks refuse to go quietly. This book, edited by Sir Derrick Dunlop and Prof. Stanley Alstead (Sir Stanley Davidson has retired from the joint editorship), is the tenth edition in 27 years. This scarcely suggests a clinging to dogma or a failure to keep up with the times in its authors, or a lack of enterprise in its publishers. For this edition nearly all the sections have been extensively revised, and several chapters have been entirely rewritten. *Pace* the iconoclasts, this textbook, at any rate, embodies medical teaching in the best tradition of the Scottish schools without slavishly adhering to tradition. Crisp writing and clear exposition are among its merits. Old textbooks, like old soldiers, may finally fade away; but not textbooks that are constantly being rejuvenated.

Price's Textbook of the Practice of Medicine (10th ed. London: Oxford University Press. 1966. Pp. 1259. 90s.).—In its youth "Price" became known for the excellence of its clinical descriptions, and popular for this and for being comprehensive but not overlong. Time never clouded its clinical vignettes; but as it grew older, during years of upsurging medical knowledge, it came in danger of falling between two stools—of becoming too lengthy for a student's standby, yet inadequate as a work of reference. Happily, in its 10th edition and 44th year, this danger seems past, and Sir Ronald Bodley Scott, the editor, can rightly claim it to be "a convenient and comprehensive survey of the art and science of contemporary British medicine". Twenty-four contributors, nine of them new, have thoroughly revised the work while preserving a pleasing and fairly uniform style of presentation, on which they and their editor are to be congratulated. A welcome change is the addition of selected references to review articles. The publishers have contributed to the transformation of the book, which now appears in a bright new two-column format. The prospects are good for a vigorous middle age.

Public Health and Social Services (6th ed. London: Edward Arnold. 1965. Pp. 166. 15s.).—This work by Dr. L. Farrer-Brown and Dr. M. D. Warren is essentially an elementary textbook describing health and social legislation and services in this country. Primarily designed for student midwives, it has proved helpful to other students needing a brief introduction to health and social services. In the five years since the previous edition administration of many services has passed from local-authority to central supervision—a trend unacceptable to many, who feel that the transfer of power to boards consisting of nominated (as distinct from elected) members is undemocratic.

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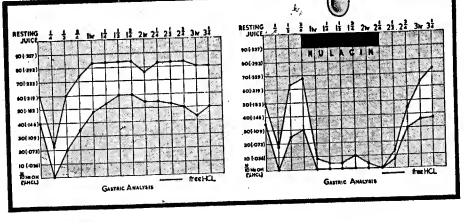

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